Citation:

Lagiou P, Sandin S, Weiderpass E, Lagiou A, Mucci L, Trichopoulos D, Adami HO. Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J Intern Med.* 2007 Apr;261(4):366-74.

PubMed ID: 17391111

Study Design:

Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine whether low carbohydrate-high protein diets are associated with increased mortality in a general population cohort of relatively young women in Sweden.

Inclusion Criteria:

- Women 30-49 years old
- Residing in Uppsala Health Care Region in Sweden during 1991-1992
- Willing to participate in the Swedish component of Scandinavian Women's Lifestyle and Health Cohort

Exclusion Criteria:

Excluded if they did not complete and return questionnaire in the pre-paid envelope provided.

Excluded:

- 16 - emigrated without re-immigration prior to start of study
- 583 - did not fill out the dietary questionnaire
- 1418 - prevalent cancer, coronary heart disease or diabetes at enrollment
- 4403 - those with missing information on any of the covariates studied
- 604 - women with energy intake outside the first (1847 kJ/day) and 99th (12474 kJ/day) percentiles

Description of Study Protocol:

Recruitment

- Women were randomly selected from 4 age strata (30-34, 35-39, 40-44, and 45-49) and invited by mail to participate in the Swedish Component of the Scandinavian Women's Lifestyle and Health Cohort.
- They were asked to fill out a questionnaire and return it in a pre-paid envelope

Design: Cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Non-nutritional covariates were used to distribute the participating women and the deaths that occurred amongst them.

- Age- and multivariate- adjusted mortality ratios were calculated
- Hazard ratios for overall mortality and mortality from cancer and cardiovascular diseases were estimated through Cox proportional hazards regression

Data Collection Summary:

Timing of Measurements

- Women were initiated in 1991-1992 and completed the lifestyle questionnaire and food frequency questionnaire.
- Observation time was calculated from date of entry into cohort until the occurrence of death, or censoring (almost 12 year follow-up)

Dependent Variables

- Mortality
- Subjects were followed in the Swedish Nationwide Health Registers using their Swedish national registration number with respect to death and emigration.
- For those women who died during the follow-up period, the cause of death was obtained from the Swedish Cause of Death Register
- Emigration Status was provided by Register of Total Population

Independent Variables

Self-administered lifestyle questionnaire assessed:

- smoking habits
- alcohol drinking habits
- anthropometry
- history of diagnosis of major diseases
- physical activity

Food frequency questionnaire:

- assessed frequency of 80 food and beverage items for the 6 months prior to enrollment
- those food and beverage items were used to determine protein intake score and carbohydrate intake score
- An inverse score, from 1 (very high carbohydrate intake) to 10 (very low carbohydrate intake) was also assigned according to the woman's decile of energy adjusted total carbohydrate intake
- Scores were added to create low-carbohydrate--high protein scores (2-20)

Control Variables

- Energy intake, saturated fat intake were controlled for in analysis

Description of Actual Data Sample:

Initial N: 49,261 women

Attrition (final N): 42,237 women

Age: 30-49 years old

Ethnicity: Swedish

Other relevant demographics:

	Number	Number of deaths	Age-adjusted mortality ratios (95% CI)	Multivariate mortality ratios (95% CI)

Education (years)				
0-10	12 537	265	1.00	1.00
11-13	16 418	183	0.67(0.55-0.82)	0.73(0.61-0.90)
>13	13 282	124	0.52(0.42-0.65)	0.63(0.50-0.78)
P-Value for trend			$<10^{-4}$	$<10^{-4}$
Physical Activity				
1 (low)	1724	50	1.00	1.00
2	4496	81	0.63(0.44-0.89)	0.75(0.52-1.06)
3	25 183	338	0.46(0.34-0.62)	0.56(0.41-0.76)
4	7227	75	0.36(0.25-0.52)	0.51(0.35-0.73)
5 (high)	3607	28	0.29(0.18-0.45)	0.39(0.25-0.63)
P-value for trend			$<10^{-4}$	$<10^{-4}$
Smoking at enrollment				
Never smoker	17 427	160	1.00	1.00
Ex-smoker	12 476	158	1.35(1.09-1.69)	1.34(1.08-1.68)
Current smoker	12 334	254	2.32(1.90-2.82)	2.07(1.69-2.54)
P-Value for trend			$<10^{-4}$	$<10^{-4}$
Alcohol intake (g/day)				
<5	31 453	415	1.00(0.83-1.21)	1.01(0.84-1.23)
5-25	10 595	148	1.00	1.00
>25	189	9	3.29(1.68-6.38)	2.59(1.32-5.09)
P-Value for trend			0.45	0.41

Anthropometrics

	Number	**Number of deaths**	**Age-adjusted mortality ratios (95% CI)**	**Multivariate mortality ratios (95% CI)**
Height (cm)				
<160	5239	90	1.00	1.00
160-164.9	11 920	159	0.78(0.60-1.00)	0.82(0.63-1.06)
165-169.9	13 538	186	0.82(0.64-1.05)	0.88(0.68-1.13)
≥170	11 540	137	0.73(0.56-0.96)	0.81(0.62-1.06)

P-value for trend			0.07	0.29
Body Mass Index (kg/m2)				
<25	30 663	366	1.00	1.00
25-29.9	9234	144	1.19(0.98-1.45)	1.08(0.88-1.31)
≥30	2340	62	2.01(1.53-2.63)	1.66(1.26-2.19)
P-value for trend			$<10^{-4}$	0.003

Location: Uppsala Health Care Region

Summary of Results:

Key Findings

Increased protein intake and decreased carbohydrate intake appear to be equally unfavorable for cardiovascular mortality.

The additive low carbohydrate--high protein score was significantly correlated:

- positively with protein intake (Spearman r=+0.35),
- inversely with carbohydrate intake (Spearman r=-0.28)
- positively with saturated lipid intake (Spearman r=+0.26)
- positively with unsaturated lipid intake (Spearman r=+0.16)
- not correlated with energy intake (Spearman r=-0.006)

The additive low carbohydrate--high protein score was positively associated with overall mortality, a 5 units increment corresponding to an increase in mortality by 11% [95% confidence interval (CI): 0-23%].

This increase in overall mortality is mostly accounted for by an increase of 37% in cardiovascular mortality (95% CI: 2-84%).

	Hazard ratios (95% CI)		
	Death from Any Cause	**Deaths from Cancer**	**Deaths from cardiovascular disease**
All women			
Lower carbohydrate (per decile)	1.06(1.00-1.12)	1.04(0.97-1.11)	1.10(0.96-1.26)
Higher Protein (per decile)	1.02(0.99-1.05)	1.01(0.96-1.05)	1.10(1.01-1.20)
Sum of above (per 2 units)	1.04(1.00-1.08)	1.02(0.96-1.08)	1.15(1.01-1.28)
Women ≤39 years old			
Lower carbohydrate (per decile)	1.09(1.00-1.18)	1.05(0.92-1.20)	1.08(0.82-1.43)
Higher Protein (per decile)	1.01(0.96-1.07)	1.01(0.94-1.10)	0.95(0.81-1.12)
Sum of above (per 2 units)	1.04(0.96-1.12)	1.04(0.92-1.15)	0.98(0.77-1.23)
Women 40-49 years old			

Lower carbohydrate (per decile)	1.05(0.99-1.11)	1.04(0.96-1.13)	1.13(0.96-1.32)
Higher Protein (per decile)	1.02(0.99-1.06)	1.00(0.95-1.05)	1.16(1.05-1.29)
Sum of above (per 2 units)	1.04(1.00-1.10)	1.02(0.94-1.08)	1.21(1.04-1.39)

Author Conclusion:

- A diet characterized by low carbohydrate and high protein intake was associated with increased total and particularly cardiovascular mortality amongst women. Vigilance with respect to long-term adherence to such weight control regimes is advisable.
- Women with lower intake of total carbohydrates and higher intake of total proteins, in comparison to those with higher intake of total carbohydrates and lower intake of total proteins, had significantly higher total mortality and, in particular, cardiovascular mortality.
- These results were more pronounced for cardiovascular mortality amongst women who at enrollment were 40 years or older and, at the end of the follow up, had reached ages between 52 and 61 years.

Reviewer Comments:

Several limitations were noted in the discussion:

- *concerns about residual confounding and the long interval between exposure ascertainment and death outcomes*
- *the long interval between exposure and outcome is a source of concern because certain individuals may change their dietary habits during the intervening period*
- *no blood cholesterol or levels or blood pressure measurements were taken at enrollment*

To add to the limitation regarding dietary patterns changing, it is possible that other variables such as physical activity patterns, smoking and alcohol intake may have changed as well during the intervening period.

Data was presented in one of the tables but the author noted that data in the table is not directly interpretable because confounding and time-to-event are not accounted for.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	???
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	???

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes

1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes

5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	???
7.1.	Were primary and secondary endpoints described and relevant to the question?	N/A
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	???
8.6.	Was clinical significance as well as statistical significance reported?	Yes

	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes